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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 08/978,637 | 11/25/1997 | ELAZAR RABBANI | ENZ-53(DIV5) | 4643 |

28171 7590 04/21/2006

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| EXAMINER | |
|---|---|
| SCHULTZ, JAMES | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 08/978,637 | RABBANI ET AL. | |
| | Examiner | Art Unit | |
| | J. D. Schultz, Ph.D. | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *318-323* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 245,248-251,253-255,260,264,265,268,270,272,284,288-290,296,299,303,304,308-313 and 317-323.

Continuation of Disposition of Claims: Claims rejected are 245,248-251,253-255,260,264,265,268,270,272,284,288-290,296,299,303,304,308-313 and 317.

## DETAILED ACTION

### *Status of Application/Amendment/Claims*

Applicant's response filed on 2 February 2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 29 July 2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Election/Restrictions*

This application contains claims 318-323 are drawn to an invention withdrawn by original presentation with traverse in the action mailed 11 February 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Claim rejections -- 35 USC § 112*

Claim 272 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, and is repeated for the same reasons of record as cited in the office action mailed 29 July 2005.

Claim 272 was previously rejected, because said claim recites the composition of claim 265 that is single-stranded. However claim 265 requires at least two stem loops in the structure.

Because stem loop structures are necessarily double stranded, the requirement of claim 272 for single-strandedness is not considered capable of being met.

Applicants have traversed the instant rejection by asserting that "'single-stranded' only refers to a single strand, and also includes a single-stranded nucleic acid having some double stranded character when there is some self hybridization within the single strand"

This argument is not considered convincing, since applicants assertion that a sequence that has some double stranded character may still be considered a single-stranded sequence runs contrary to the accepted definition of the prior art. Since applicants do not appear to have provided a more specific definition which explicitly states that a single-stranded molecule may contain some double stranded character while still being considered a single-stranded molecule, it is maintained that the plain meaning of "single-stranded" is that which is not double stranded.

Claims 253 and 254 recite the limitation "said signal processing sequence" in claim 245. There is insufficient antecedent basis for the term "processing" in these claims.

Claim 308 recites the limitation "said complementary specific nucleic acid sequence" in claim 299. There is insufficient antecedent basis for this limitation in the claim.

Claim 317 recites the limitation "said tertiary nucleic acid is RNA" in claim 245. There is insufficient antecedent basis for this limitation in the claim.

Claim 272 recites the limitation "gene product" in claim 265. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 101***

Claims 245, 248, 249, and 251, 253-255, 260, 264, 299, 303, 304, 308-313 and 317 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, and is repeated for the same reasons of record as cited in the office action mailed 29 July 2005.

The rejection of claims 245, 248, 249, and 251, 253-255, 260, and 264, are based upon the breadth of the claim language, which previously read: "a composition comprising a primary nucleic acid component, which upon introduction into eukaryotic cell synthesizes a secondary nucleic acid which synthesizes a gene product, or a tertiary nucleic acid, or both, in said eukaryotic cell, wherein said primary nucleic acid is not obtained with said secondary or tertiary nucleic acid or said gene product". Such language was considered to read on non-statutory subject matter, because a human is considered to be a composition comprising a primary nucleic acid that has the claim limitations. The claims as cited above were also considered to read on nonstatutory subject matter as reading on products of nature. The claim language has now been amended to read "A nucleic acid construct...", which applicants assert does not read on a human or a product of nature.

These arguments are adopted in regards to the amended claims reading on a human, but it is maintained that the claims continue to read on a product of nature, since the instant claims read on a chromosome is undergoing replication and is therefore a product of nature. This is because a chromosome could be considered a primary nucleic acid, which acts as a template for the synthesis of a secondary nucleic acid (the daughter chromosome), which acts a template for the

synthesis of a gene product which is could be a sense RNA. The rejection is maintained therefore.

Claims 299, 303, 304, 308-313 and 317 were similarly rejected as reading on nonstatutory subject matter, i.e., both a human and a product of nature.

Prior to the instantly submitted amendment, independent claim 299 recited "A nucleic acid which upon introduction into a eukaryotic cell produces more than one specific nucleic acid, each such specific nucleic acid produced being substantially nonhomologous with each other and being either complementary with the specific portion of one or more viral or cellular RNAs in a cell or binds to a specific viral or cellular protein."

In response, applicants have amended the preamble to recite "a multi-cassette nucleic acid construct comprising either more than one promoter or when the initiator or both", and assert that this amendment is "certainly not a product of nature or human being."

These arguments are adopted in regards to the amended claims reading on a human, but it is maintained that the claims continue to read on a product of nature. The claims read on a chromosome which is undergoing replication and is therefore a product of nature, because a chromosome can be considered a multi-cassette nucleic acid construct, which certainly comprises more than one promoter, which produces more than one specific nucleic acid, which are substantially nonhomologous with each other and are complementary to a specific portion of one or more cellular RNA targets, since a chromosome is double stranded and therefore comprises the antisense strand. The rejection is maintained therefore.

***Claim Rejections - 35 USC § 102***

Claims 245, 248-251, 253-255, 260, and 264, are rejected under 35 U.S.C. 102(b) as being anticipated by Bebenek et al. (J. Biol. Chem. 1989. 264(28)16948-16956), and is repeated for the same reasons of record as set forth in the action mailed 29 July 2005.

The instant claims are drawn to compositions which comprise a primary nucleic acid construct, which when introduced into eukaryotic cells, act as a template for the synthesis of a second nucleic acid, which then act as a template for the synthesis of a sense or an antisense nucleic acid, wherein the primary nucleic acid is not obtained with said secondary nucleic acid or said gene product, and wherein said composition further comprises a signal sequence.

These claims were rejected over Bebenek et al., who teaches that HIV virions reproduce imperfectly, which result in an average of five mutations per genome per round of replication. Essentially, the fact that Bebenek indicates that an average of five mutations occurs per round of replication is considered to indicate that the final product is mutated compared to the primary nucleic acid, which satisfies the limitation that the primary nucleic acid is not obtained from the secondary nucleic acid or gene product. Accordingly, Bebenek et al. teaches a primary nucleic acid construct, i.e. the HIV virion, which gives rise to a secondary nucleic acid, which in turn gives rise to a sense nucleic acid, which is the virus containing an average of five mutations, and is therefore considered to be different and thus not obtained from the primary nucleic acid construct. Clearly, since the sense nucleic acid contains promoters terminators etc., it is also considered to comprise a signal sequence, thus meeting all the limitations of the above claimed invention.

Applicants dispute this by asserting that Bebenek et al. is not a study on in vivo HIV replication, and rather, occurs in an artificial system. Applicants point to the abstract statement of Bebenek "if operative in vivo" which applicants suggest casts doubt as to whether the "gene product" element of the claim would be any different from the primary nucleic acid when the construct is expressed in a cell, a situation which is expressly disclaimed in the recited invention.

This is not considered convincing, because A) the system of Bebenek et al. utilizes all the components utilized in the HIV replication process, indicating that such components would act identically in the cell, and B) there is no evidence that further suggests that the system would behave any differently inside a cell. In fact, the phrase "if operative in vivo" is offered by Bebenek as support merely for the rate of mutation, and does not cast doubt as to whether HIV mutates. This is because, as one of ordinary skill would understand, the rate of mutation is attributed exclusively to the fidelity of the polymerase enzyme, a property which is not affected by whether the enzyme if functioning in a cell or not. At no point does Bebenek cast doubt on whether or not this process occurs in a cell, because it is well accepted that HIV mutates from its original form. Bebenek et al. merely says that if the rate they see in their assay operates in vivo at the same rate observed in their studies, than the average virion contains 5 mutations. The prima facie case of anticipation is satisfied with this teaching. It is applicants' responsibility to provide evidence or reasoning as to why a process that occurs in the presence of all critical cellular components would not otherwise occur inside the cell, and mere assertions to the contrary will not take place of such evidence or reasoning.

Applicants also argue that the reported error rate of HIV reverse transcriptase of 5 mutations per genome would result in a situation where "it is likely that one would obtain some

genomes with no mutation." Applicants argue that the mere fact that a certain thing may result from a given set of circumstances is insufficient to prove anticipation, and the rejection should be withdrawn accordingly.

This is not considered convincing. Bebenek does not teach that mutations "may" occur. Bebenek et al. teaches that they *do* occur, at a rate of about 5 mutations per replication. While it may not be out of the realm of possibility to assert that HIV replication has occurred error-free at some point in time, this does not mitigate the fact that mutations have and do occur. Applicants have not provided any evidence or reasoning beyond mere assertion that refutes that Bebenek et al. teaches that mutations occur during HIV replication, and that such mutations are inherent to the process of HIV replication. The rejection is maintained therefore.

Claims 265, 268, 270, 284, and 288-290, and 296 are rejected under 35 U.S.C. 102(b) as being anticipated by Izant, J et al. (Chimeric antisense RNAs. Raven Press Series on Molecular and Cellular Biology (1992), 1(Gene Regul.), 183-95).

Claims of the instant invention are drawn to a nucleic acid construct which encodes a secondary nucleic acid which comprises a nuclear localization sequence comprising a portion of snRNA, which has at least two stem loops present at the 3' end of the native snRNA and also a reimportation signal, and an antisense. The antisense may consist of DNA, RNA, a DNA-RNA hybrid, a DNA-RNA chimera, and the combination of the foregoing, or wherein the nuclear localized sequence comprises a portion of U1 RNA comprising C and D loops, as well as cells, biological systems, and methods of use thereof.

Izant et al. teaches a nucleic acid construct which encodes a secondary nucleic acid which comprises a nuclear localization sequence comprising a portion of snRNA, which has at least two stem loops present at the 3' end of the native snRNA and also a reimportation signal, and an antisense. The antisense may consists of RNA, and the nuclear localized sequence comprises a portion of U1 RNA comprising C and D loops. Izant et al. also teaches cells, biological systems, and methods of use thereof. See figure 1, for example.

Claims 299 and 303, 304, and 308-313 are rejected under 35 U.S.C. 102(b) as being anticipated by Junker et al. (Antisense Res Dev. 1994 Fall;4(3):165-72.), and is repeated for the same reasons of record as cited in the action mailed 29 July 2005.

The instant claims were rejected previously because Junker et al. discloses the use of a vector comprising sequences encoding two different antisense oligos targeted to HIV. Thus, Junker et al. teaches a nucleic acid which produces more than one specific nucleic acid which are nonhomologous with each other and are complementary to a specific portion of an RNA target.

Applicants traverse the rejection by arguing that Junker et al. do not teach all the limitations of the instant claims because only one transcript is actually expressed. This is considered to be incorrect, particularly when taking into account the teachings of figures 1A and 1C. Figure 1A teaches a sequence that encodes two distinct antisense sequences; the first is DCT5T-α tat, and the second is DCT5T-α rev. Figure 1C teaches that the two antisense sequences are separate. Thus, contrary to applicant's arguments, the construct of Junker et al. produces more than one specific nucleic acid transcript as required by the instant claims. Furthermore, the claim language requires "either more than one promoter or one initiator or

both". While it is agreed that such language stipulates that more than one promoter is required, there is no such requirement that the modifier of "more than one" is also directed to "initiator". Thus, one interpretation is that there need be only one initiator, which is considered to be taught by Junker et al. Claims 310 and 311 are rejected because they limit embodiments not required in the claims (i.e. they limit recitations recited in the alternative in the independent claim, and thus not required in the dependent claims).

## *Conclusion*

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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JDS

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER